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# Treatment of refractory secondary hyperparathyroidism with ethanol injection: The importance of glandular volume

**Walter G. Douthat, Santiago E. Orozco, Javier de Arteaga, and Pablo U. Massari**

*Bone and Mineral Metabolism Section, Renal Service, Hospital Privado-Centro Médico de Córdoba; Postgraduate School of Nephrology, Catholic University of Córdoba, Argentina; and Department of Radiology, Hospital Privado-Centro Médico de Córdoba, Córdoba, Argentina*

**Treatment of refractory secondary hyperparathyroidism with ethanol injection: The importance of glandular volume.**

*Background.* Percutaneous ethanol injection treatment (PEIT) has been proposed as an alternative to surgery for patients with secondary hyperparathyroidism. The present study was undertaken to determine factors that may predict results.

*Methods.* We performed PEIT in 19 patients with secondary hyperparathyroidism refractory to medical therapy under ultrasonographic guidance in an ambulatory facility with local anesthesia. Biochemical assays were performed immediately before the last dialysis session (basal) and between 1 to 7 days after PEIT (post-PEIT).

*Results.* Serum PTH, calcium, and phosphorus levels decreased significantly after treatment. The percent of change in serum PTH was significantly correlated to total nodular volume ($r = 0.73$, $P = 0.0004$), and basal PTH levels ($r = 0.48$, $P = 0.03$). Post-PEIT serum phosphate and calcium x phosphate product disclosed negative correlations that were statistically significant with the decrease of PTH levels ($r = -0.60$, $P = 0.009$, and $r = -0.60$, $P = 0.01$, respectively). The total nodular volume was significantly correlated to the percent change in serum calcium levels ($r = 0.60$, $P = 0.01$), in phosphate levels ($r = 0.64$, $P = 0.009$), and calcium x phosphate product ($r = 0.66$, $P = 0.01$).

*Conclusion.* Our findings suggest that patients with uncontrolled secondary hyperparathyroidism may benefit from PEIT if they present with very high basal PTH levels and/or big nodule size.

One of the main problems nephrologists face when treating chronic renal failure patients is to control the increased secretion of parathyroid hormone during dialysis and after renal transplantation [1–5]. Great progress has been achieved in this field in terms of medical therapy. However, there are still a large number of patients in whom the metabolic disorder cannot be controlled and for whom parathyroidectomy is indicated.

Percutaneous ethanol injection treatment (PEIT) has been proposed as an alternative to surgery for these patients. Successful nodule destruction depends on several factors, but the population eligible for treatment with PEIT has not been completely defined [6–13].

We report our experience with PEIT in patients with chronic renal failure and secondary hyperparathyroidism refractory to medical therapy. We analyze response to treatment with relation to biochemical parameters, nodule characteristics, and technical aspects of the procedure.

## METHODS

PEIT was performed in 19 patients with end-stage renal disease (ESRD) and secondary hyperparathyroidism refractory to medical therapy. All patients received hemodialysis three times a week, with a mean duration of 85.8 ± 10.1 months of dialysis therapy.

One patient had undergone subtotal parathyroidectomy and suffered recurrent hyperparathyroidism in the remaining portion of the gland. His clinical condition made him unsuitable for further surgery.

The criteria chosen to perform the treatment were: symptomatic bone disease associated to PTH levels higher than 300 pg/mL, lack of responsiveness to calcitriol pulse therapy (either oral or intravenous), discontinuation of calcitriol due to hypercalcemia (serum Ca >11 mg/dL), hyperphosphatemia (serum P >6 mg/dL), or a calcium x phosphorous product higher than 65. The possibility of aluminum overload was ruled out by bone biopsy, serum aluminum levels lower than 20 μg/L, lack of recent exposure to aluminum-containing phosphate binders, or to high levels of aluminum in the dialysate. The size of all glands treated with PEIT was larger than 0.1 $cm^3$ as calculated by ultrasonographic evaluation of their three longest axes.

In those patients with extremely altered clinical and biochemical features, a 99mTc Sestamibi scintigraphy was performed to discard the presence of ectopic parathyroid tissue.

**Key words:** PEIT, renal osteodystrophy, chronic renal failure, hemodialysis.

**Table 1.** Ultrasonographic, PEIT, and biochemical data

| Ultrasonography and PEIT data | Mean ± SE | | |
|---|---|---|---|
| Nodules/patient *N* | 1.8 ± 0.2 | | |
| Total nodule size/patient $cm^3$ | 1.5 ± 0.4 | | |
| Size/gland $cm^3$ | 0.9 ± 0.2 | | |
| Injections/patient *N* | 2.0 ± 0.2 | | |
| Ethanol volume/patient $cm^3$ | 3.4 ± 0.5 | | |
| Biochemical data | Basal Mean ± SE | Post-PEIT Mean ± SE | *P* value |
| PTH *pg/mL* | 1184.5 ± 154.1 | 683.1 ± 84.3 | 0.0002 |
| Serum calcium *mg/dL* | 10.5 ± 0.4 | 9.3 ± 0.4 | 0.02 |
| Serum phosphate *mg/dL* | 6.8 ± 0.4 | 5.8 ± 0.4 | 0.05 |
| Calcium x phosphate product $mg/dL^2$ | 70.8 ± 4.2 | 53.5 ± 4.5 | 0.02 |
| Alkaline phosphatase *UI/L* | 957.4 ± 286.3 | 1005.4 ± 314.4 | |

PEIT was performed under ultrasonographic guidance in an ambulatory facility. All injections were administered by the same qualified interventional radiologist. A 95% ethanol solution was used for PEIT, with total alcohol volume calculated to be the same as the nodule volume. Local anesthesia with lidocaine was used. All patients gave their informed consent to the procedure. In each session one or more injections were performed according to the anatomic characteristic of the glands.

Biochemical assays were performed immediately before the last (basal) dialysis session and between 1 to 7 days after the PEIT (post-PEIT).

Calcium, phosphorus, and alkaline phosphatase were measured in an autoanalyzer (Hitachi 917; Hitachi, Ltd., Tokyo, Japan), and intact parathyroid hormone (PTH) by electrochemiluminiscence (Nichol's Institute, San Juan Capistrano, CA, USA).

For statistical analysis, Student *t* test for continuous variables and Pearson correlation were used. $P < 0.05$ was considered statistically significant.

## RESULTS

Table 1 shows biochemical data and the number of nodules per patient, the total nodule volume per patient, the number of injections per patient, and the alcohol volume used for each nodule per patient. Thirty-four glands in 19 patients were treated by 38 sessions of PEIT.

There was a significant (33.3% ± 5.6%) decrease in PTH levels, from a mean of 1184.5 ± 154.1 pg/mL (basal PTH) to 683.1 ± 84.3 (post-PEIT) ($P = 0.0002$) (Table 1), along with a decrease in serum levels of calcium and phosphorous, and the calcium x phosphate product.

The percent change in serum PTH was significantly correlated to total nodular volume ($r = 0.73$, $P = 0.0004$), and basal PTH levels ($r = 0.48$, $P = 0.03$) (Fig. 1 A and B).

Serum phosphate and calcium x phosphate products post-PEIT disclosed changes that were both negative and significantly correlated to the decrease in PTH levels ($r = -0.60$, $P = 0.009$ and $r = -0.60$, $P = 0.01$, respectively).

The total nodular volume was significantly correlated to the percent change of serum calcium levels ($r = 0.60$, $P = 0.01$), in phosphate levels ($r = 0.64$, $P = 0.009$) (Fig. 2 A and B), and calcium x phosphate products ($r = 0.66$, $P = 0.01$).

Ten of the 19 patients had only minor complications related to PEIT; seven patients experienced neck discomfort, which ceased immediately after the procedure. One patient developed minor hypocalcemia, but responded well to intravenous calcium administration. Another patient reported a short duration of swallowing discomfort, and another patient had a transient dysphonia.

## DISCUSSION

The medical treatment of bone disease due to secondary hyperparathyroidism in patients with end-stage renal failure has recently improved [14–20]. However, in an important number of cases [21], this pathology is still problematic due to lack of responsiveness to therapy, or, more frequently, discontinuation secondary to hypercalcemia, hyperphosphatemia, or both. Surgical parathyroidectomy usually results in an immediate reduction in parathyroid hormone levels, as well as clinical and histologic bone improvement both short- and long-term [22, 23]. Nonetheless, this kind of therapy is not completely safe. Besides the surgical risk these patients may present, there is also the possibility of recurrent hyperparathyroidism or, more frequently, the development of adynamic bone disease [24].

Since the early 1980s, PEIT has been proposed as a less invasive alternative to parathyroidectomy, but results have not been always satisfactory. A possible reason for this is that indications for this technique have not been clearly established [6–13].

In this series we report a change in PTH and improvement in serum calcium, phosphate, and calcium x phosphate product, which was clearly correlated to basal PTH levels and to nodule volume.

Patients with large nodule volume and very high basal

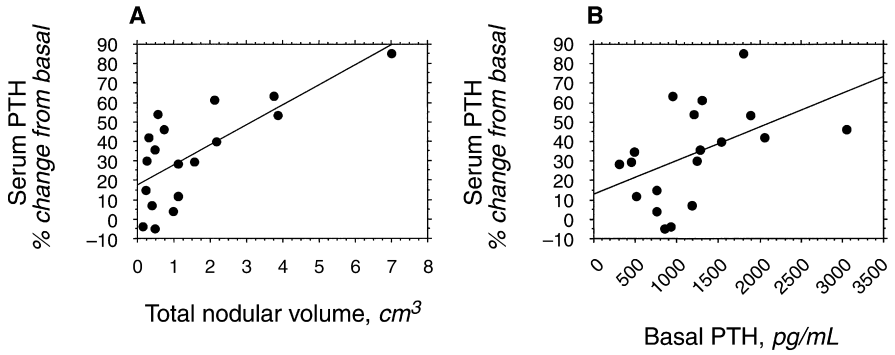


**Fig. 1. Correlation between percent reduction of PTH and *(A)* total nodular volume or *(B)* basal PTH.**

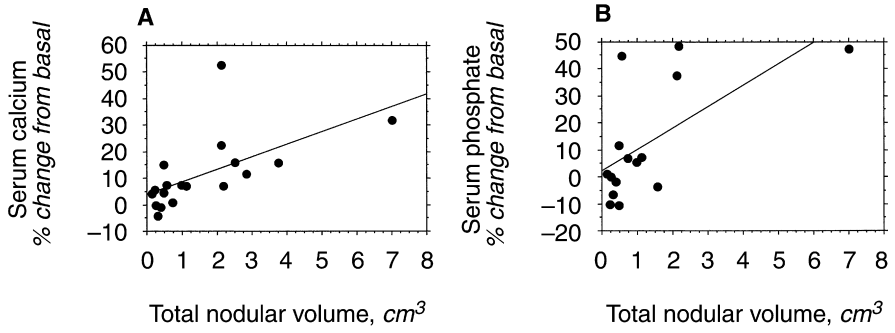


**Fig. 2. Correlation between percent reduction of (*A*) calcium and (*B*) phosphate and total nodular volume.**

PTH levels were those who obtained the best results after PEIT.

Other researchers have obtained varying results. Kakuta et al [10] obtained a decrease of more than 50% in PTH levels in 80.4% of their patients. Giangrande et al [6, 7] found a similar decrease in 26% of their patients. Such differences may be due to variations in patient characteristics, the PEIT technique, and PTH assays utilized.

Gland size is directly related to increased parathyroid hormone secretion [11, 25]. It is possible that the better response in patients with higher basal PTH levels and larger glands was due to a better localization and optimized injection precision by ultrasonography [26]. The larger size also may have helped achieve a better technical precision. Other groups have already pointed out the importance of gland size [11, 25, 26]. It has been shown that patients who have undergone parathyroidectomy are more refractory to calcitriol pulse therapy when their glands are larger [25]. Also, it is important to consider that the degree of hyperplasia is different in each patient and among the same patient's four glands. Thus, it is difficult to know exactly which gland or glands are affecting each patient, and to what extent each gland is affected. More recently, the existing difficulties in achieving a positive response to calcitriol in patients with gland sizes larger than 0.5 to 1 cm or 0.5 $cm^3$ have been described [25]. A similar frequent recurrence rate has been observed when parathyroid tissue of the previous size is autografted after a total parathyroidectomy [25]. This information is in agreement with our findings, since gland size was an important factor in determining responsiveness to treatment. These results suggest that to obtain a good response to PEIT, patients should have big nodules and/or high basal PTH levels. Our experience concurs with Fukagawa et al [26] in that gland size is an important factor to consider when deciding upon the management of parathyroid glands.

In this series, all responsive patients showed symptomatic clinical improvement almost immediately (data not shown). As shown by Giangrande et al [7], all patients with a positive symptomatic response to treatment presented an immediate decrease in PTH levels. An initial PTH decrease was also evident in only 2 of 10 patients within the group of non-responsive patients. Our patients showed significant improvement in calcemia, phosphatemia, and calcium x phosphate product levels (Table 1), which allowed us to extend and intensify medical therapy. A post-parathyroidectomy decrease of serum phosphate has been described, especially in patients with very high levels of PTH and alkaline phosphatase before surgery. This may be related to the degree of severity of osteitis fibrosa prior to the treatment [27]. The treatment with phosphate binders and calcitriol was adequately continued in our responsive patients. This represents an additional benefit of this technique.

## CONCLUSION

Our findings suggest that with the application of PEIT, patients respond satisfactorily if they present with high basal PTH levels and a considerable gland size. We propose to use it as a first step to control refractory secondary hyperparathyroidism. In other cases, the indications are less clear, but due to the low probability of complications, simplicity of the technique, and low cost, PEIT should be considered when nodular parathyroid enlargement is found on ultrasonagraphic examination.

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*Reprint requests to Walter Guillermo Douthat, Bone and Mineral Metabolism Section, Renal Service, Hospital Privado–Centro Médico de Córdoba, Naciones Unidas 346 (5016), Córdoba, Argentina.*
*E-mail: wdouthat@powernet.net.ar*

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